Common Drug Review
Pharmacoeconomic Review Report

September 2017

Drug	Omalizumab (Xolair)
Indication	For adults and adolescents (12 years of age and above) with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.
Reimbursement Request	As per indication
Dosage Form(s)	Sterile powder for reconstitution for subcutaneous injection, 150 mg vial
NOC Date	November 18, 2004
Manufacturer	Novartis Pharmaceuticals Canada Inc.

Omalizumab (Xolair) Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in ***allergy and immunology*** who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary drug reimbursement recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AQLQ	Asthma Quality of Life Questionnaire
CDR	CADTH Common Drug Review
CDEC	Canadian Drug Expert Committee
CEA	cost-effectiveness analysis
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
LABA	long-acting beta$_2$-agonist
LAMA	long-acting muscarinic receptor antagonist
LTRA	leukotriene receptor antagonist
NICE	National Institute for Health and Care Excellence (UK)
OCS	oral corticosteroid
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PHARMAC	Pharmaceutical Management Agency (New Zealand)
PITT	primary intention-to-treat
QALY	quality-adjusted life-year

SUMMARY

Background

Omalizumab is being reviewed for the treatment of adults and adolescents (12 years of age and older) with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen, and whose symptoms are inadequately controlled with inhaled corticosteroids.[1]

Omalizumab is available as a 150 mg single-use vial of sterile powder for reconstitution for subcutaneous injection at a cost of $612 per vial (Ontario Drug Benefit Formulary Exceptional Access Program, January 2016).[2] At the recommended dose of 150 mg to 375 mg administered subcutaneously every two or four weeks,[1] the annual cost of omalizumab ranges from $7,956 to $47,736.

Omalizumab was originally submitted to the CADTH Common Drug Review (CDR) for this indication in April 2005; however, a final recommendation by the Canadian Expert Drug Advisory Committee (CEDAC) was not issued since a request for reconsideration from the manufacturer was deemed to include new information requiring resubmission.[3] Omalizumab was subsequently resubmitted by the manufacturer to CDR in October 2005, resulting in a CDEC recommendation of Do not Reimburse. The reasons for the recommendation were that three of the four blinded randomized controlled trials suggested no statistically significant improvements in acute asthma exacerbations leading to hospitalizations, emergency room visits, or physician visits, and only one of the trials was in a patient population treated with inhaled corticosteroids (ICS) with a long-acting beta$_2$-agonist (LABA). Although all of the trials reported that omalizumab improved quality of life, CDEC noted that, at the submitted price, omalizumab was not cost-effective.[4] In 2015, omalizumab was reviewed by CDEC for adults and adolescents with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment. It received a recommendation of Reimburse with Clinical Criteria and Conditions, with one of the conditions being a substantial price reduction.[5]

Approach to This Review

The current CDR review was undertaken in response to a request from the drug plans that participate in the CDR review process asking that the use of omalizumab in asthma be re-reviewed in light of the availability of new clinical evidence. The manufacturer of omalizumab was invited to submit clinical and/or economic information, but was not obligated to do so. The manufacturer did not provide an economic model for the relevant population, although it did provide the submitted pharmacoeconomic report describing the results of the cost-effectiveness analysis of omalizumab for the treatment of moderate-to-severe asthma that had been provided in their April 2005 submission to CDR.[6] However, the resubmission for omalizumab in October 2005, which culminated in the final CEDAC recommendation,[7] was based on an economic evaluation that was a revision of the one originally submitted. CDR requested the revised analysis from the manufacturer for the current review, but it was not provided.

As CDR was unable to undertake reanalyses on an economic model, CDR considered the report provided by the manufacturer in the same manner as published literature and appraised the information. To supplement the information provided by the manufacturer, CDR also undertook a literature review of published economic studies of patients with moderate-to-severe persistent asthma comparing omalizumab to ICS, either alone or in combination with a LABA, with or without other controller medications (i.e., a long-acting muscarinic receptor antagonist, leukotriene receptor antagonist [LTRA]), or with mepolizumab, the anti-IL-5 drug.

Cost Comparison

The clinical expert consulted by CDR confirmed that omalizumab would be used as an add-on to an optimized regimen of conventional controller medications for patients with inadequate symptom control; thus, the most appropriate comparator for omalizumab was determined to be no additional treatment, placebo or as-needed acute administration of rescue medications such as oral corticosteroids (OCS). Since omalizumab is expected to be more effective and more costly than these comparators, the most appropriate form of analysis is a cost-utility analysis or cost-effectiveness analysis. Mepolizumab, a recently approved biologic treatment for severe eosinophilic asthma, may be an appropriate comparator for omalizumab for a subset of patients with inadequately controlled asthma; it was not considered a comparator for the present review, as it is currently under review by CDR and not yet listed by CDR-participating drug plans.

The expected number of vials of omalizumab used per administration in this population varies based on body weight (kg) and immunoglobulin E (IgE) level.[1] A review of IMS Brogan PharmaStat data indicates that, over the last five years, the average number of units per claim ranged from 2.32 to 2.35, although the average dosing in the EXTRA and AUS23 trials indicates an average dose of approximately 2.85 to 3.05 vials per four-week period.[8,9] In most (if not all) provinces that reimburse omalizumab, the unit size is a vial. The PharmaStat data and the trials suggest that the annual cost per patient may range from $15,912 (two single-use vials per four-week period) to $31,824 (four single-use vials per four-week period).

Summary of the Published Economic Information

The CADTH CDR undertook a review of published Health Technology Assessments (HTA) and recommendations from HTA agencies, as well as a review of the economic literature of omalizumab in patients with moderate-to-severe persistent allergic asthma. The economic literature search, undertaken by an information specialist, identified 272 economic abstracts, of which 33 received full text review. Studies conducted from the Canadian perspective were of greatest interest, and only one published article (Brown et al., 2007)[10] met this criterion. This study is briefly summarized subsequently, with a more complete review provided in Appendix 2. Several other economic studies were identified; however, these were undertaken for other countries (including several European countries, Japan, Brazil, the US, and the UK); thus, their generalizability to the Canadian setting is uncertain. Several international HTA agencies have reviewed omalizumab for this indication, including the Pharmaceutical Management Agency (New Zealand), the Scottish Medicines Consortium (Scotland), the National Institute for Health and Care Excellence (NICE) (UK) and the Pharmaceutical Benefits Advisory Committee (Australia). The results of these HTA reviews are briefly reported subsequently, with a more complete summary in Appendix 3. The manufacturer provided a copy of the 2005 pharmacoeconomic report submitted to CDR.[6] This was reviewed alongside the existing literature, as was the recommendation by CEDAC.

Brown et al.[10] assessed the cost-effectiveness of omalizumab in addition to standard therapy (defined as high-dose ICS plus a LABA [plus additional controller medication if required]) compared with standard therapy alone over a lifetime time horizon in patients with severe persistent asthma despite treatment with high-dose ICS plus LABA. The study stated that Canada was used as the reference country; however, results were reported in euros (C$1 = €0.70) and a subpopulation was chosen based on a European dataset (ETOPA study), using a model based on the Swedish setting. Efficacy data from the ETOPA study were used to populate the model. Brown et al. reported an incremental cost-effectiveness ratio (ICER) of €31,209 (C$44,584)[11] per quality-adjusted life-year (QALY). At a willingness-to-pay threshold of €35,000 (C$50,000), the probability that omalizumab was cost-effective was reported to be

69.7%. One-way sensitivity analyses found the ICER ranged from €23,762 to €66,443 per QALY (C$33,946 to C$94,919), with the largest differences from the base-case result arising from changes to the discount rate for future costs and QALYs, and exclusion of the asthma-associated mortality rate. Brown et al. noted that their study was limited due to: the assumptions made in extrapolating one-year study data to the lifetime time horizon; treatment adherence not being considered; and the assumption that future events were independent of previous ones (which may favour standard therapy). They also noted that their results differed from other published economic analyses that populated models with data from the INNOVATE trial, in that other economic analyses reported higher ICERs for omalizumab compared with standard therapy.[10]

The 2005 pharmacoeconomic submitted report, while dated, indicated that a trial-based evaluation over a 28-week time horizon resulted in an incremental cost of $53,000 per clinically significant exacerbation avoided, while the manufacturer's modelled evaluation, which was based on one-year real-world data, resulted in an incremental cost of approximately $13,000 per clinically significant exacerbation avoided.[6] The observation, that the incremental cost per clinically significant exacerbation avoided was lower when the analysis was based on an uncontrolled real-world study, aligns with the results reported by Brown et al.[10] CDR was not able to validate the manufacturer's results, as the model was not provided. However, CDR noted several limitations in the report that suggested the results may be biased in favour of omalizumab, including: the time horizon; the higher severity of the asthma within the patient population included in the trial (severe, persistent allergic asthma) compared with the indication (moderate-to-severe asthma); and uncertainty regarding the appropriateness of the primary intention-to-treat population. The final CEDAC recommendation for omalizumab for the treatment of asthma noted that the manufacturer's pharmacoeconomic submission (which was not available to CDR for the current review) reported an ICER of $63,000 per QALY, with a range of $35,000 to $219,000 per QALY. However, the committee felt that the rates of asthma exacerbation in the analysis potentially overstated the benefits of omalizumab, and that the true cost-effectiveness of omalizumab was "likely to be much less favourable."[12]

New Information Since 2006

CDR identified six trials published since 2006. Based on the CDR assessment, while omalizumab was effective in reducing exacerbations, emergency room visits, and hospitalizations, the findings were not consistent across all studies. CDR found limited evidence that omalizumab reduced the use of ICS and rescue medication (short-acting $beta_2$-agonists), and noted that any clinical improvements seen with omalizumab did not appear to translate into improvements in patients' quality of life. Overall, the available evidence suggests adding omalizumab to existing background treatment in patients with moderate-to-severe persistent allergic asthma in Canada may produce improvements in some important asthma-related outcomes, although the consistency and magnitude of effect is uncertain. No new or notable safety concerns were identified.

Given the findings from CDR, the lack of an active comparator, and updated cost information, a cost-effectiveness analysis would be required to accurately assess the impact of the new clinical findings for the patient population requested.

Issues for Consideration

CDR identified the following issues for consideration:

- There is the potential for off-label use of omalizumab for patients with perennial allergic rhinitis, allergic bronchopulmonary aspergillosis, atopic dermatitis, food allergies, or severe non-allergic asthma. Use outside the Health Canada–approved indication would further increase drug budgets.

Conclusions

The current CDR clinical review of omalizumab found that, in patients with moderate-to-severe persistent allergic asthma who are inadequately controlled with ICS or ICS plus LABA with or without other asthma controllers, adding omalizumab to existing background treatment might produce improvements in some important asthma-related outcomes, although the consistency and magnitude of effect is uncertain. However, in the absence of an economic model, CDR was unable to comment on the cost-effectiveness of omalizumab in light of the new clinical information. The available information from previous manufacturer submissions to CDR suggests that cost-effectiveness was likely overestimated. Internationally, HTA agencies have generally accepted that omalizumab is effective in certain populations, but costly (typically based on revisions to the manufacturer's analyses). To understand the implications of the new clinical information (of varying consistency and magnitudes of effect) on the cost-effectiveness of omalizumab, a cost-effectiveness analysis is required.

The published price of omalizumab is a $612 per vial; the annual cost varies substantially based on the Health Canada–approved treatment regimen, ranging from $7,956 for a patient receiving one vial per month to $47,736 for a patient receiving three vials every two weeks.

APPENDIX 1: COST COMPARISON TABLE

The clinical expert consulted by CDR deemed the comparator treatments presented in Table 1 to be appropriate. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR OMALIZUMAB FOR THE TREATMENT OF PATIENTS WITH MODERATE-TO-SEVERE ALLERGIC ASTHMA

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Omalizumab (Xolair)	150 mg	Vial (sterile powder for reconsti-tution)[a]	612.0000[b]	612.00 to 1,836.00	150 mg to 375 mg is administered SC every 2 or 4 weeks[c]	Low dose: 21.80 High dose: 130.78	Low dose: 7,956.00 High dose: 47,736.00

IgE = immunoglobulin E; SC = subcutaneous.
[a] Omalizumab is available as a single-use vial; if a full vial is not used, then the remaining dose is discarded. Thus, wastage needs to be incorporated.
[b] Price of omalizumab sourced from the Ontario Drug Benefit Formulary Exceptional Access Program (January 2016).[2] The published formulary price in Alberta is lower ($600).[13]
[c] Dosing is dependent upon body weight and baseline IgE. Dosing can range from 150 mg to 300 mg every four weeks, and 225 mg to 375 mg every two weeks.[1]

Additional treatments for asthma are located in Appendix 4.

The following treatments indicated in a similar patient population have recently been reviewed or are currently being reviewed by CDR, but are not yet listed by any plans; thus, no price is available: fluticasone furoate (Arnuity Ellipta), tiotropium (Spiriva Respimat), and mepolizumab (Nucala).

APPENDIX 2: REVIEW OF THE EXISTING LITERATURE

CDR undertook a review of the economic literature for the use of omalizumab in patients with asthma. The search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; PubMed; and the University of York Centre for Reviews and Dissemination National Health Service (NHS) Economic Evaluations Database. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were omalizumab and derivatives (e.g., Xolair), monoclonal antibodies and derivatives, and asthma and related terms.

Methodological filters were applied to limit retrieval to economic studies. The search was run on December 17, 2015. Retrieval was not limited by publication year or language.

Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on April 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist (www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), which includes the websites of health technology assessment agencies and other economics-related resources. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer was contacted for information regarding unpublished studies.

The search identified 272 abstracts, of which 33 were retrieved for full text review (including 11 abstracts) based on the following list of inclusion criteria:

- cost-effectiveness or cost-minimization study that included omalizumab
- population was patients with moderate-to-severe persistent allergic asthma
- study assessed comparative effectiveness, where the comparator treatment was omalizumab or inhaled corticosteroid (ICS) with or without a long-acting beta$_2$-agonist [LABA], long-acting muscarinic receptor antagonist, or leukotriene receptor antagonist [LTRA]
- Canadian perspective.

The only citation that met the inclusion criteria was a study by Brown et al. reporting a cost-effectiveness analysis of omalizumab (in addition to standard therapy compared with standard therapy alone) in patients with severe persistent asthma despite high-dose ICS plus LABA, using Canada as the reference country.[10] This study is summarized subsequently. Several other economic studies were identified; however, these were undertaken for other countries (including several European countries, Japan, Brazil, the US, and the UK);[14-27] thus, their generalizability to the Canadian setting is uncertain.

Brown et al. 2007[10]

Brown et al. 2007 undertook a study to assess the cost-effectiveness of omalizumab in addition to standard therapy compared with standard therapy alone in patients with severe persistent asthma despite high-dose ICS plus LABA.[10] The study stated that Canada was used as the reference country,

although results were reported in euros and a subpopulation was chosen based on the European label population for omalizumab. The model was based on a previously published Markov model assessing the cost-effectiveness of omalizumab in the Swedish setting.[28] Clinical data were based on a subpopulation of a one-year open-label trial of omalizumab (ETOPA study).[29]

The health states in the Markov model were: day-to-day asthma (periods with no clinically significant non-severe or severe exacerbations); clinically significant non-severe exacerbation; and clinically significant severe exacerbation. The model also considered death from all causes, and asthma-related death due to severe exacerbations. A lifetime time horizon was used, although patients received omalizumab only for the first five years.

In ETOPA, clinically significant exacerbations were defined as asthma worsening, requiring treatment with systemic corticosteroids. Severe exacerbations were not recorded in ETOPA; thus, the distribution of these events was derived from the INNOVATE study. Future events were assumed independent of previous events. Omalizumab responders were defined as patients with an improvement of 0.5 points or greater in the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) score. As no deaths occurred in the ETOPA study, the risk of exacerbation-related death from clinically significant severe exacerbation was based on data from a community-based study by Lowhagen et al. (1997), in which mortality rate was estimated to be 3.108%).[30] Estimated mortality risk was the same regardless of treatment in the base case, although a sensitivity analysis was undertaken to test a different rate with omalizumab (2.48%). The risk of all-cause death for the general Canadian population (0.12%) was sourced from Statistics Canada.[31]

To obtain utility values, Mini-AQLQ results from ETOPA were mapped to the EuroQol 5-Dimensions Questionnaire for daily symptoms at baseline (week 0) and end of study (week 52). Utilities for the exacerbation states were obtained from a prospective study conducted in the UK.[32]

The model included costs for exacerbations, drug treatment, and routine visits. The costs were reported in euros (C$1 = €0.7). There was some uncertainty as to the costing of exacerbations, as exacerbation-related resource use was stated to have been based on the ETOPA study, while resource use for severe and non-severe exacerbation-related events was derived from the INNOVATE study. The average costs of severe exacerbations and non-severe exacerbations used in the analysis were €260.90 and €177.60, respectively. The cost inputs were not well defined, although it was noted that the Ontario Schedule of Benefits and Fees and the Canadian Institute for Health Information were used to determine resource and hospitalization costs. Administration costs were not included in the base case (as these costs were covered by a Novartis support program), but were included in a sensitivity analysis. Societal costs were not included. The total cost of omalizumab (€11,634 [C$16,620; 27.7 vials over the 52 weeks]) was based on data from ETOPA. The annual cost of standard therapy was €1,938 (C$2,769). Costs were discounted at 5% per annum. Although not explicitly stated, it appears that QALYs were also discounted at 5% per annum. The year in which the costs were current was not reported.

The authors reported that the total lifetime discounted costs and QALYs for patients on standard therapy alone were €27,403 (C$39,147) and 6.49, respectively. Omalizumab added an additional cost of €33,854 (C$48,363) for an additional 1.08 QALYs, resulting in an ICER of €31,209 (C$44,584) per QALY. The probabilistic sensitivity analysis indicated a 95% confidence interval (CI) of €27,739 to €40,840 (C$39,627 to C$58,343). At a willingness-to-pay threshold of €35,000 (C$50,000), the probability that omalizumab was cost-effective was 69.7%. One-way sensitivity analyses found the ICER ranged from

€23,762 to €66,443 (C$33,946 to C$94,919) per QALY, with the main drivers being discounting of future costs and QALYs, and the exclusion of the asthma-associated mortality rate.

The authors noted that their ICER was considerably lower than the ICER reported from the Markov model for omalizumab in Sweden (€56,091 [C$80,130] per QALY), which was based on data from the INNOVATE study.[28] The authors noted that the data from ETOPA may be more representative of treatment results in clinical practice due to the setting of the study.

The following limitations were identified by the authors:

- data from ETOPA over one year were extrapolated over a lifetime time horizon and non-trial data were used to estimate asthma-related mortality due to limitations of the ETOPA data
- 100% adherence to treatment was assumed; therefore, discontinuation was not considered in the model, although this was unlikely to favour one group over another
- future events were independent of previous events (whereas numerous publications have shown that previous events are strongly correlated with future events), which likely favoured standard therapy in the model.

Manufacturer-Submitted Report

In addition to the published information, CDR undertook a brief summary and appraisal of the pharmacoeconomic report submitted by the manufacturer to CDR. The same pharmacoeconomic report was included in the manufacturer's original submission to CDR in April 2005.

The manufacturer's aim was to evaluate the cost-effectiveness of omalizumab in Canada in adults and adolescents with severe, persistent allergic asthma whose symptoms are inadequately controlled despite the best available therapy. The primary analysis presented was a cost-effectiveness analysis (CEA) to determine the cost per clinically significant exacerbation avoided in adults and adolescents with severe persistent asthma who receive omalizumab as add-on therapy to best standard care (based on GINA 2002, Step 4 asthma patients)[33] compared with patients receiving best standard care alone, over a lifetime time horizon. A secondary CEA was also undertaken to determine the cost of an increase of 0.5 points or more in quality of life score. A subgroup analysis was undertaken in patients with severe persistent asthma and a history of two or more exacerbations in the 14 months prior to initiating treatment with omalizumab. An analysis was also undertaken comparing omalizumab with best standard care alone in patients with moderate-to-severe asthma over a one-year time horizon using real-world data from the ETOPA study.[29] All analyses were undertaken from the perspective of the Canadian health care system.

Both the primary and secondary economic analyses were undertaken as trial-based analyses from a multi-centre, 28-week, randomized, double-blind, placebo-controlled clinical trial (INNOVATE).[34] INNOVATE evaluated the efficacy of omalizumab as add-on therapy in severe persistent allergic asthma patients with poorly controlled symptoms despite best standard care (which included ICS and LABAs, as well as OCS, LTRAs, theophyllines, or oral beta$_2$-agonists).[33] The reported primary end point in the trial was clinically significant asthma exacerbations, while secondary outcomes included emergency visits (hospital admissions, emergency room visits and unscheduled physician visits) as well as asthma-related quality-of-life scores measured using the AQLQ.

The results of the primary intention-to-treat (PITT) population were used in the model. The manufacturer selected a trial-based analysis because: a prospective, lifetime model was not considered appropriate due to the limited amount of long-term data available on clinical outcomes with

omalizumab treatment (at the time, the longest study comparing omalizumab with best standard care had a duration of one year); few deaths are expected to occur from asthma over a patient's lifetime; and because quality-of-life data in the form of utility measurements were not available to estimate QALYs. At the time of analysis, there was no algorithm available to convert the disease-specific AQLQ scores into utility scores (0 to 1 scale), which form the basis for QALYs; therefore, the secondary analysis was based on the reported minimal clinically important difference for AQLQ of 0.5 points,[35] which was a secondary end point in the INNOVATE study.

Resource use was estimated from resource use captured in the clinical trial. The manufacturer's submitted price of omalizumab was $600 per vial. Direct resource use and costs included in the economic calculation included medication usage (study drug, rescue medication, other asthma-related concomitant therapies including medications for adverse events) and asthma exacerbation management. Costs for all rescue and other asthma-related medications were sourced from IMS Brogan data and the British Columbia drug formulary. Clinically significant exacerbations were categorized as either self-managed (patients managed at home with previously provided medication), an unscheduled physician visit, a visit to the emergency room, or admission to hospital. Costs for lab tests and procedures resulting from exacerbations were sourced from the Ontario Schedule of Benefits and Fees. Hospitalization costs were determined from the Canadian Institute for Health Information case-mix group 146 (primary diagnosis of asthma). Costs for an emergency room visit were sourced from a prospective study that evaluated the total management costs of emergency room visits for acute asthma in Vancouver, Canada.[36] A parametric Poisson regression analysis of data from INNOVATE was used to calculate 95% CIs around the primary and secondary outcome measures. The 95% CIs around the cost components were tested using gamma distributions and use of non-parametric bootstrapping techniques. Wherever possible, patient-level data from the trial were used to construct CIs around the mean cost estimates. Costs were reported in 2004 Canadian dollars.

Mean asthma treatment costs for PITT patients treated with omalizumab were $80 per patient per day compared with $18 per patient per day for those in the placebo group. The manufacturer reported that in the primary base-case analysis, the number of clinically significant exacerbations (in all health care settings combined) per patient was reduced from 0.91 (95% CI, 0.73 to 1.14) in the placebo group to 0.68 (95% CI, 0.53 to 0.87) in the omalizumab treatment group (difference of 0.23; 95% CI, 0.20 to 0.27), based on a Poisson regression analysis.[6] With respect to the secondary base-case analysis, 61% of patients in the omalizumab group attained an improvement in AQLQ scores of at least 0.5 points, compared with 48% in the placebo group.

The results of the manufacturer's model for the primary base-case analysis showed that the mean incremental cost per clinically significant exacerbation avoided was $52,996 (95% CI, $17,459 to $89,121) over seven months. The cost per ≥ 0.5-point increase in AQLQ score in the same population was $93,762 (95% CI, $27,741 to $134,825). The subgroup analyses for the population with severe persistent asthma and two or more exacerbations in the previous 14 months found that the cost per clinically significant exacerbation avoided was $58,305 (95% CI, $21,624 to $98,684) and the cost per ≥ 0.5-point increase in AQLQ score in the same population was $111,131 (95% CI, $29,511 to $168,533). The subgroup analysis using data from the ETOPA study over a one-year time horizon found the cost per clinically significant exacerbation avoided was reduced substantially ($12,830; 95% CI, $3,465 to $28,983). The cost per ≥ 0.5-point increase in AQLQ score was still high ($63,723; 95% CI, $33,970 to $107,436).

The following limitations of the analyses presented in the report were noted:

- The analysis was a trial-based evaluation over a period of only 28 weeks. Asthma is a chronic condition; thus, patients are likely to require treatment over a longer period of time than the time horizon presented in the manufacturer's economic analyses. The impact of a longer time horizon on the analysis is unknown, but treatment with a costly medication over a longer period would substantially increase the incremental treatment costs.
- Only patients with severe asthma were considered in the manufacturer's submitted economic analysis (see INNOVATE inclusion criteria); the approved indication for omalizumab includes patients with moderate asthma. The cost-effectiveness for the entire indicated population, i.e., moderate-to-severe asthma, is unknown, but omalizumab may be less cost-effective in patients with less severe asthma due to lower absolute reductions in exacerbation rates.
- Data for clinical efficacy and resource use were taken from the PITT population of the INNOVATE trial. It is uncertain whether data taken from the regular intention-to-treat population would be different, and what the impact would be of not using these data for the analysis.

As the underlying model was not provided by the manufacturer, CDR was unable to validate the results presented in the report.

The CADTH CDR noted that the original CDR submission of omalizumab for asthma was withdrawn by the manufacturer before a CEDAC drug recommendation was issued, but omalizumab was resubmitted some months later. The economic analysis provided with the resubmission was different from the one provided with the original submission. In February 2006, CEDAC recommended that omalizumab not be reimbursed for adults and adolescents with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled with ICS.[37] The economic analysis provided by the manufacturer for the current review appears to be the one provided as part of the original submission (as described in the 2006 CDEC recommendation), rather than the revised analysis provided with the resubmission. Upon request, the manufacturer did not provide the revised analysis for the current review. The 2006 CEDAC recommendation noted that omalizumab costs approximately $1,200 per patient per month, and that the manufacturer reported a mean ICER of $63,000 per QALY (sensitivity analyses resulted in a range from $35,000 to $219,000). CEDAC noted that the rates of asthma exacerbation might have been overestimated in the pharmacoeconomic model, which significantly overestimated the true cost-effectiveness of omalizumab. CEDAC indicated that omalizumab was not cost-effective at the current price.

APPENDIX 3: PUBLISHED HEALTH TECHNOLOGY ASSESSMENT REPORTS

Omalizumab for the treatment of severe persistent asthma has been reviewed by several international Health Technology Assessment (HTA) agencies, including New Zealand's Pharmaceutical Management Agency (PHARMAC), the Scottish Medicines Consortium (SMC), the National Institute for Health and Care Excellence (NICE) in the UK, and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. The PHARMAC and SMC recommendations are provided narratively in the following paragraphs, while the NICE and PBAC recommendations are provided in Table 2 and Table 3.

At the November 2013 meeting, the Pharmacology and Therapeutics Advisory Committee recommended that PHARMAC fund omalizumab for the treatment of severe asthma in patients aged 6 years and older with a medium priority following the development of Special Authority criteria, with strict entry and exit criteria and the facility for a trial of treatment.[38,39] The published price of omalizumab was $500 per vial, with an understanding that a confidential rebate would apply that would reduce the net price of the treatment.[39]

After an initial rejection (December 2006),[40] omalizumab was accepted — in September 2007 — for restricted use within Scotland's National Health Service (NHS) as add-on therapy to improve asthma control in adult and adolescent patients 12 years of age and older with severe persistent allergic asthma who have been prescribed chronic systemic steroids and for whom all other treatments have failed.[41] Treatment response is to be assessed at 16 weeks and treatment discontinued in patients who have not shown a marked improvement in overall asthma control. In March 2010, SMC advised that the restricted population for omalizumab was extended to include children (from age 6 to < 12 years).[42] In May 2011, SMC advised that omalizumab solution for injection (75 mg, 150 mg) was accepted for use within NHS Scotland (replacing the previously approved powder and solvent for injection) for adults, adolescents 12 years of age and older and children from 6 to < 12 years of age with convincing immunoglobulin E (IgE)–mediated asthma who are prescribed chronic systemic steroids and for whom all other treatments have failed.[43]

Omalizumab was initially considered for listing for severe persistent allergic asthma in all patients by NICE 2007[44] and in children aged 6 to 11 in 2010.[45] The most recent NICE guidance is shown in Table 2.

TABLE 2: HEALTH TECHNOLOGY ASSESSMENT FINDINGS (NICE)

	NICE (April 2013)[46]
Study drug and regimen	OMA (Xolair) 75 mg and 150 mg vials, administered as 75 mg to 600 mg every two or four weeks, up to a maximum dosage of 600 mg every two weeks
Price	£256.15 per 150 mg (C$412.73); £128.07 per 75 mg (C$206.36); excluding value-added tax. Cost per year range: £1,665 to £26,640 (C$2,682 to $42,925)
Population	Add-on therapy to improve control of asthma in adults and adolescents aged 12 years and over, and children aged 6 to 11 years with severe persistent allergic asthma who have: a positive skin test or in vitro reactivity to a perennial aeroallergen, reduced lung function (FEV_1 of > 80%, adults/adolescents), frequent daytime symptoms or nighttime awakenings, and multiple documented severe exacerbations despite daily high-dose ICS + LABA.

	NICE (April 2013)[46]
Modelled populations	Two separate base-case populations: • adults and adolescents (mean age approximately 40 years) • children (mean age 9 years). Two subgroups: • people hospitalized in the year before model entry • people receiving maintenance OCS when entering model.
Treatment	OMA + SOC
Comparators	ICS + SOC (rescue treatment) ICS + LABA
Perspective	NHS and personal social services
Discount rate	3.5% per annum for both costs and health outcomes
Model structure and patient flow	• Markov model structure, hypothetical cohort, lifetime time horizon (up to 100 years), 10 years of OMA. • People enter at base HS (day-to-day asthma). Treatment response measured at 16 weeks (end of first cycle); if respond to OMA, then remain on OMA for treatment duration. • For subsequent cycles, people remain in base HS or experience an exacerbation. • Both asthma-related and non-asthma–related death were modelled. • After non-fatal exacerbations, people return to base HS.
Data sources	• Treatment response and exacerbation rates based on the values for each treatment from clinical trials (base case: INNOVATE for adults/adolescents, and IA-05 for children; scenario analyses: EXALT and APEX [adults/adolescents only]). • Asthma-related death occurs only during severe exacerbation, as derived from Watson et al., 2007. • Administration costs were estimated in the model based on assumption of specialist nurse taking 10 minutes to administer OMA (rate = £47/hour). SOC required two outpatient visits per year, OMA + SOC required four. • Cost of exacerbations were based on rates in the trials and included general physician visits, outpatient specialist appointments, emergency room admissions, rehab, ward stays, ICU. • Utilities values were derived by mapping AQLQ scores from INNOVATE to EQ-5D.
Manufacturer's results	• Adults/adolescents: deterministic ICER = £32,076/QALY (C$51,684); probabilistic ICER = £33,268/QALY (C$53,605). • Children: deterministic ICER = £80,747/QALY (C$130,108); probabilistic ICER = £88,998/QALY (C$143,402). • Manufacturer estimated the probability that OMA is cost-effective in adults/adolescents at £20,000 (C$32,226), and £30,000/QALY (C$48,339), to be 0.005 and 0.267 respectively. • SAs for adults and adolescents indicated the ICER to be as high as £72,113/QALY (C$116,195). For children, the ICER increased as high as £662,893/QALY (C$1,068,119). • For the hospitalized subgroup, for adults and adolescents, ICER ranged from £27,928 to £35,198/QALY (C$45,000 to C$56,715); and for children, £65,100/QALY (C$104,896). • For the OCS subgroup, for adults and adolescents, ICER ranged from £26,320 to £37,604/QALY (C$42,409 to C$60,591). This analysis could not be undertaken for children.

	NICE (April 2013)[46]
Issues noted by the review group	• The manufacturer assumed no treatment waning, though results from studies indicate OMA effect waned. • The manufacturer assumed no QoL benefits prior to age 12, which the AG noted might not be appropriate. Direct EQ-5D measurement was also noted to be more appropriate than mapping of AQLQ values. • The AG considered asthma-associated mortality; relationship between mortality, age, and severity of exacerbations; degree of HRQoL improvements with OMA; and the influence of age on ICER had not been adequately addressed. The AG considered asthma-related mortality to be overestimated. The AG reanalyses focused on assumptions for asthma-related mortality and HRQoL. The AG considered the most appropriate source for asthma-related mortality to be Vries et al., 2010. The AG revised monitoring assumptions.
Results of reanalyses by the review group	• Adults/adolescents: ICER = £83,822/QALY (C$135,062); Children: ICER = £78,009/QALY (C$125,696). AG estimated probability OMA is cost-effective at £30,000/QALY (C$48,339) was 0% in both populations. • For the hospitalized subgroup, ICER was £46,431/QALY (C$74,814) for adults and adolescents, and £44,142/QALY (C$71,126) for children. For this subgroup, AG estimated probability OMA is cost-effective at £30,000/QALY (C$48,339) was 0% in both populations. • For the OCS subgroup, ICER was £50,181/QALY (C$80,856) for adults and adolescents. AG reported probability OMA is cost-effective at £30,000/QALY (C$48,339) was 0%. • The AG commented that key drivers of ICER were: asthma-related mortality rates, degree of HRQoL improvement from OMA and, for those taking maintenance OCS, whether or not AEs from OCS are included. • Appraisal committee requested further reanalyses from the AG, some of which required further data from the manufacturer, for 3 new populations: 1. people with very severe persistent allergic asthma maintained on OCS and hospitalized in year before treatment 2. same as 1, but who were not necessarily hospitalized in the year before treatment 3. people with very severe persistent allergic asthma who were on maintenance or frequent courses of OCS (4+ courses per year), but had not necessarily been hospitalized in the year before treatment. • The AG also incorporated revised assumptions for asthma-related mortality (Watson et al.); AEs for OCS; 5-year treatment duration for children and 10-year treatment duration for adults/adolescents; EQ-5D utility values from EXALT used for all populations; exacerbation rates at start of treatment; treatment effectiveness; and HRQoL was assumed to be the same for children as for adults/adolescents. • ICER for children ranged from £61,096 to £62,945/QALY (C$98,443 to C$101,423). ICER for adults/adolescents ranged from £31,573 to £32,508/QALY (C$50,873 to C$52,380). • When adult, adolescent and children were combined, ICER was similar to adult/adolescent results (range: £32,229 to £33,150/QALY) (C$51,931 to C$53,415). The ICER was above £30,000/QALY (C$48,339) in all SAs. • The manufacturer provided additional analyses for populations 2 and 3 with a revised asthma-related mortality rate, while also revising the proportion of children in the AGs age-weighted ICERs (range 2.2% to 7.3%). The manufacturer also agreed to a patient access scheme (via price discount). The manufacturer's revised ICERs included some errors on review from the AG, which recalculated the

	NICE (April 2013)[46]
	ICERs and found they ranged from £23,626 to £24,008/QALY (C$38,069 to C$38,684) for population 2, and £23,001 to £23,395/QALY (C$37,061 to C$37,696) for population 3.
Recommendation	NICE recommends omalizumab as possible additional treatment to standard asthma therapy for some people aged 6 years and over with a certain type of severe persistent allergic asthma and requiring continuous or frequent treatment with OCS (at least 4 courses in the last year).

AE = adverse event; AG = Assessment Group; AQLQ = Asthma Quality of Life Questionnaire; C$ = Canadian dollar; EQ-5D = EuroQol 5-Dimensions Questionnaire; HRQoL = health-related quality of life; HS= health state; ICER = incremental cost-effectiveness ratio ($/QALY); ICS = inhaled corticosteroids; ICU = intensive care unit; FEV_1 = forced expiratory volume in one second; LABA =long-acting $beta_2$-agonist; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OCS = oral corticosteroids; OMA = omalizumab; QALY = quality-adjusted life-year; QoL = quality of life; SA = sensitivity analysis; SOC = standard of care.
Note: Currency conversion rate was as follows: 2013 £ to 2013 CAD, £1 = $C1.6113. (www.bankofcanada.ca/rates/exchange/annual-average-exchange-rates/, accessed January 7, 2016).[11]

TABLE 3: HEALTH TECHNOLOGY ASSESSMENT FINDINGS (PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE)[a]

	November 2009[47]	November 2010[48]
Study drug	Omalizumab (Xolair), powder for injection, 150 mg	
Price	Not stated	
Population	Initial and continuing treatment of patients with uncontrolled severe allergic asthma who are aged 12 years or older and who meet certain criteria	
Comparators	• Placebo (if uncontrolled, resistant, or unresponsive to, or unable to use OCS) • OCS	• Optimal asthma therapy (essentially, the same comparator as November 2009 submission)
Perspective	Public payer	
Discount rate	5% (costs and outcomes)	
Model structure and patient flow	• 10 health states, including OMA response, and OCS use. • Model events included: non-asthma death, response/non-response, discontinue OCS, maintenance OCS, and exacerbations (clinically significant, severe, hospitalized severe, or fatal). Patients cycled through the model in 32-week cycles over 50 years.	• Updated economic evaluation, based on data from Trial 2306 and Trial 2425 • CEA (trial-based cost per exacerbation avoided and per additional patient free of exacerbation) and CUA presented.
Data sources	Not reported	
Notes on the economic analysis	• The model is sensitive to health state utilities used. Using EQ-5D utilities (per guidelines) increased ICER, as opposed to utilities derived using the AQLQ. • For OCS population, the ICER range was A$45,000QALY and A$75,000/QALY (C$40,361 to C$67,268). • For non-OCS population, the ICER range was A$75,000/QALY and A$105,000/QALY (C$67,268 to C$94,175). • The model is also sensitive to: the probability of maintaining OMA response long-term; risk of asthma-associated death;	• ICERs for omalizumab vs. placebo based on Trial 2306 and Trial 2425 were in the range of A$45,000/QALY to A$75,000/QALY (C$42,615 to C$71,025). • PBAC noted the model was most sensitive to: risk of asthma-associated death; relative risk of death for OCS; and model duration; price of OMA; and utility values used. • PBAC deferred a reimbursement decision to seek further price reduction from sponsor. PBAC received price reduction for which the resulting base-case ICER

	November 2009[47]	November 2010[48]
	relative risk of death for OCS; and model duration.	was reduced to a range of A$40,000/QALY to A$45,000/QALY (C$37,880 to C$42,615).
Recommendation	• PBAC rejected the submission because of a poorly targeted restriction, uncertain clinical benefit, and a high and unacceptable cost-effectiveness ratio	• PBAC recommended reimbursing OMA on the basis of an acceptable cost-effectiveness ratio in a severe patient group with limited treatment options whose asthma was uncontrolled while on at least 10 mg/day prednisolone equivalent

A$ = Australian dollar; AQLQ = Asthma Quality of Life Questionnaire; C$ Canadian dollar; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; EQ-5D = EuroQol 5-Dimensions Questionnaire; ICER = incremental cost-effectiveness ratio; OCS = oral corticosteroids; OMA = omalizumab; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year.

[a] At the November 2014 PBAC meeting, the PBAC secretariat considered expanding the reimbursement restriction wording for OMA based on utilization rates.[49] The consideration did not include an assessment of any changes in cost-effectiveness for OMA. PBAC recommended expanding the restriction to align optimal asthma therapy with current clinical guidelines and to extend the period for assessment of response from two weeks to four weeks.

Note: Currency conversion rates were as follows: For 2009 A$ to 2009 C$, A$1 = C$0.8969; for 2010 A$ to 2010 C$, A$1 = C$0.9470 (www.bankofcanada.ca/rates/exchange/annual-average-exchange-rates, accessed January 21, 2016).[11]

APPENDIX 4: OTHER POTENTIAL COMPARATOR TREATMENTS

TABLE 4: COST COMPARISON TABLE FOR OTHER TREATMENTS (ICS, ICS/LABA COMBINATIONS AND LTRAS) FOR PATIENTS WITH ALLERGIC ASTHMA

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
ICS							
Fluticasone propionate (Flovent HFA)	50 mcg 125 mcg 250 mcg	MDI (120 doses)	23.9300 41.2800 82.5400	0.1994 0.3440 0.6878	100 mcg/250 mcg/ 500 mcg twice daily	0.80 to 2.75	291.15 to 1,004.24
Fluticasone propionate (Flovent Diskus)	50 mcg 100 mcg 250 mcg 500 mcg	Inhalant powder (60 doses)	NA 23.9300[a] 41.2800 64.2000	NA 0.3988 0.6880 1.0700	100 mcg/250 mcg/ 500 mcg twice daily	0.80 to 2.14	291.15 to 781.10
Ciclesonide (Alvesco)	100 mcg 200 mcg	Actuation inhalation (120 doses)	45.5400 75.2800	0.3795 0.6273	100 mcg/200 mcg twice daily	0.76 to 1.25	277.04 to 457.95
Mometasone furoate (Asmanex Twisthaler)	200 mcg 400 mcg	Inhalant powder (60 doses)	35.4800 70.9600	0.5913 1.1827	200 mcg/400 mcg once daily	0.59 to 1.18	215.84 to 431.67
Budesonide (Pulmicort Turbuhaler)	100 mcg 200 mcg 400 mcg	Inhalant powder (200 doses)	31.2700 63.8600 93.0000	0.1564 0.3193 0.4650	100 mcg/200 mcg/ 400 mcg twice daily	0.31 to 0.93	114.14 to 339.45
Beclomethasone dipropionate (QVAR)	50 mcg 100 mcg	MDI (200 doses)	31.1900 62.2000	0.1560 0.3110	Total dose of 100 mcg to 800 mcg, twice daily	0.31 to 2.49	113.84 to 908.12
ICS/LABA combinations							
Fluticasone furoate/ vilanterol trifenatate (Breo Ellipta)	100 mcg/25 mcg 200 mcg/25 mcg	Inhalant powder (30 doses)	120.000 NA	4.0000 NA	100 mcg/25 mcg or 200 mcg/25 mcg once daily	4.00 NA	1,460.00 NA
Budesonide/ Formoterol (Symbicort Turbuhaler)	100 mcg/6 mcg 200 mcg/6 mcg	Inhalant powder (120 doses)	64.5600 83.8800	0.5380 0.6990	100 mcg/6 mcg or 200 mcg/6 mcg twice daily	1.08 to 1.40	392.74 to 510.27
Fluticasone propionate/ Salmeterol (Advair)	125 mcg/25 mcg 250 mcg/25 mcg	MDI (120 doses)	97.4299 138.3141	0.8119 1.1526	125 mcg/25 mcg or 250 mcg/25 mcg twice daily	1.62 to 2.30	592.69 to 841.41
Fluticasone propionate/ Salmeterol (Advair Diskus)	100 mcg/50 mcg 250 mcg/50 mcg 500 mcg/50 mcg	Inhalant powder (60 doses)	81.3929 97.4299 138.3141	1.3565 1.6238 2.3052	100 mcg/50 mcg or 250 mcg/50 mcg or 500 mcg/50 mcg twice daily	2.71 to 4.61	1,185.40 to 1,682.82

Drug/ Comparator	Strength	Dosage Form	Price ($)	Price/ Dose ($)	Recommended Daily Use	Daily Drug Cost ($)	Annual Cost ($)
Mometasone furoate/ Formoterol fumarate (Zenhale)	50 mcg/5 mcg 100 mcg/5 mcg 200 mcg/5 mcg	MDI (120 doses)	70.5600 89.5560 108.5400	0.5880 0.7463 0.9045	100 mcg/10 mcg 200 mcg/10 mcg 400 mcg/10 mcg twice daily	2.35 to 3.62	858.48 to 1,320.57
LTRAs							
Montelukast (Singulair)	4 mg 5 mg 10 mg	Tablet	1.5264[a] 1.6902[a] 2.4823[a]	1.5264 1.6902 2.4823	Age 6–14: 5 mg daily Age 15+: 10 mg daily	1.69 to 2.48	616.92 to 906.04
Montelukast (generics)	4 mg 5 mg 10 mg	Tablet	0.3646[a] 0.5565[a] 0.8195[a]	0.3646 0.5565 0.8195	Age 6–14: 5 mg daily Age 15 +: 10 mg daily	0.56 to 0.82	203.12 to 299.12
Zafirlukast (Accolate)	20 mg	Tablet	0.7766[a]	0.7766	20 mg twice daily	1.55	566.92

ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist; MDI = metered dose inhaler; NA = not available.

[a] Alberta Health Drug Benefit List (January 2016).[13]

Source: Ontario Drug Benefit Formulary (accessed January 2016), unless otherwise indicated. [50]

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